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(54) Title: PHARMACEUTICAL COMPOSITIONS

(57) Abstract

The invention provides a solid pharmaceutical dosage form comprising: (i) cimetidine; and (ii) antacid, wherein at least part of the antacid is in the form of granules comprising a freely water-soluble solid diluent, the antacid, and a rapidly swellable water-insoluble disintegrant. Compositions of this type overcome the problem of the reduced bioavailability of cimetidine which can occur when cimetidine is co-administered with antacids.

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PHARMACEUTICAL COMPOSITIONS

This invention relates to a solid pharmaceutical dosage form comprising cimetidine and an antacid and to a method for the preparation of such a dosage form.

Cimetidine is a histamine H_2-antagonist which has been described in U.K. Patent Specification 1,397,436. Cimetidine has been shown to be useful in the treatment of duodenal, gastric, recurrent and stomal ulceration, and reflux oesophagitis and in the management of patients who are at high risk from haemorrhage of the upper gastro-intestinal tract.

Cimetidine and antacids are frequently co-administered (see for example the article by H. Allgayer and G. Paumgartner, Arzneim Forsch. pp.870-871, 34, No. 8 (1984)). The rationale for co-administration is that antacid brings about rapid relief from the symptoms of excess stomach acidity by neutralising the acid whereas the cimetidine brings about more sustained relief by inhibiting secretion of more acid.

However, it is well known (see Allgayer and Paumgartner, and Steinberg et al, New England J. Medicine, 1982; 307, 400-4) that when cimetidine is co-administered with antacids, particularly aluminium hydroxide and magnesium hydroxide, there is frequently a substantial reduction in the bioavailability of the cimetidine. The reason for the reduction in bioavailability is not clear, although a number of attempts to discover the mechanism responsible for the problem have been reported in the literature. Thus for example Allgayer and Paumgartner were unable to demonstrate why the decrease in bioavailability occurs

although they indicated that it was not due to binding of the cimetidine by the antacid.

The benefits, particularly in terms of patient compliance with a treatment regimen, which would arise from an effective combination product containing cimetidine and an antacid, would be expected to be considerable. However, the problem of loss of bioavailability, and the lack of understanding of its cause have, up until now, precluded the development of such a product, as far as we are aware.

It has now been found, surprisingly, that the problem of the loss of bioavailability of the cimetidine can be solved by granulating at least part of the antacid separately, and in a particular manner, prior to mixing with the cimetidine.

In a first aspect, therefore, the invention provides a solid pharmaceutical dosage form comprising:

(i) cimetidine; and

(ii) antacid, wherein at least part of the antacid is in the form of granules comprising a freely water-soluble solid diluent, the antacid, and a rapidly swellable water-insoluble disintegrant.

It is preferred that at least 50% by weight of the total antacid in the dosage form is granulated in the particular manner described above in (ii). In general, as the ratio of antacid to cimetidine is increased, it is

desirable to increase the proportion of antacid granulated in this way. In one preferred embodiment of the invention, substantially all of the antacid is thus granulated.

The term "freely soluble" is known in the art as referring to a particular level of solubility; thus, in the U.S. Pharmacopoeia, it is defined as meaning that a substance can form a 10% solution in a solvent. Preferably the substance can form at least a 50% solution in water.

Typically the freely water-soluble solid diluent is a sugar and/or sugar alcohol.

Examples of sugars and sugar alcohols are sucrose, lactose, sorbitol, xylitol and mannitol, preferred diluents being lactose, sorbitol and sorbitol/lactose mixtures.

It is preferred that the ratio (w/w) of solid diluent to antacid is in the range 1:1 to 8:1, particularly approximately 3:1.

Typically the rapidly swellable water-insoluble disintegrants are synthetic or semi-synthetic polymers of a type known in the art as superdisintegrants (see for example International Patent Application No. PCT/US 87/00302, published as WO 87/05804, and references cited therein). Examples of superdisintegrants include cross-linked polymeric disintegrants such as cross-linked carboxymethyl celluloses, particularly croscarmellose sodium and croscarmellose calcium, cross-linked polyvinyl pyrrolidone, and sodium starch glycolate.

Typically the disintegrant is present in an amount from approximately 0.5% (w/w) to approximately 8% (w/w), relative to the total weight of the granules, particularly approximately 2% (w/w).

The antacid-containing granules are preferably formed by a dry granulation process, for example by compacting using a roller compacter or a tablet press, followed by milling the compact to give granules that have low friability. Suitably, in such a case, the mixture for granulating can contain a lubricant. Examples of lubricants are stearates such as magnesium stearate, and stearic acid.

The antacid typically is selected from aluminium hydroxide, magnesium hydroxide, magnesium carbonate, calcium carbonate and co-dried gels, for example aluminium hydroxide-magnesium carbonate co-dried gel. A particular antacid is aluminium hydroxide or a mixture of aluminium hydroxide and magnesium hydroxide.

In general a dosage form contains between 5 mEq and 30 mEq of antacid, and preferably approximately 14 mEq.

The cimetidine will usually be present in an amount from 50 mg to 800 mg per dosage form, and typically a dosage form will contain 100 mg or 200 mg of cimetidine.

Examples of dosage forms include tablets, capsules and lozenges.

The compositions of the present invention can be in the form of chewable tablets, that is to say tablets which disintegrate readily in the mouth when chewed. With chewable tablets, the pronounced bitter taste of cimetidine means that in practice it is necessary to

provide a means of masking the bitter taste. One means of masking the bitter taste is to coat the cimetidine with a coating agent in an amount effective to mask the bitter taste but which does not significantly affect the bioavailability of the cimetidine.

One such coating agent is dimethylaminoethyl-methacrylate/methacrylic acid ester co-polymer which is sold under the trade name Eudragit E. According to a co-pending patent application (reference no. 11940) claiming priority from British patent applications Nos. 8710965 and 8710966, cimetidine can be granulated using Eudragit E, in an amount 2 - 20% (w/w) relative to the cimetidine, as the granulating agent. By employing a Eudragit E loading in this range, the bitter taste of cimetidine is masked but the dissolution characteristics and hence bioavailability remain acceptable.

In addition to cimetidine and antacid-containing granules, the solid dosage forms of the present invention can contain other pharmaceutical excipients. Thus, for example, where the dosage form is subject to a compression step, the dosage form can additionally contain a lubricating agent, typically stearic acid or a stearate salt and particularly magnesium stearate.

The compositions of the present invention can also contain additional sweeteners, for example aspartame, cyclamate and saccharin, and colouring and flavouring agents as known in the art.

The invention will now be illustrated in greater detail by the following Examples.

EXAMPLE 1

100 mg Chewable Tablet

Ingredient	mg/tablet	%w/w
Cimetidine Premix Granules		
Cimetidine	100.0	90.9
Eudragit E100*	10.0	9.1
Antacid (Al/Mg) Granules		
Direct Compression Sorbitol	590.0	34.01
Direct Compression Lactose		
Crystalline	325.0	18.73
Spray dried	325.0	18.73
Croscarmellose Sodium Type A	30.0	1.73
Dried Aluminium Hydroxide Gel**	250.0	14.41
Magnesium Hydroxide**	200.0	11.53
Magnesium Stearate	15.0	0.86
	1735.0	100.00

Tableting Mix for Compression	mg/tablet
Cimetidine Premix Granules	110.0
Antacid (Al/Mg) Granules	1735.0
Aspartame	3.0
Peppermint	15.0
Tutti Frutti	5.0
Spearmint	5.0
Lactose	200.0
Croscarmellose Sodium Type A	30.0
Magnesium Stearate	15.0
	2118.0

* Added to the cimetidine by granulation as a 40% w/v solution in methylene chloride. Solvent lost in processing.

** Quantities used adjusted for the potencies of raw materials:
Standard quantity of Dried Aluminium Hydroxide gel is equivalent to 117.5 mg/tablet Al_2O_3 or 180 mg/tablet Aluminium Hydroxide ($Al(OH)_3$).

Process Description

A 40% w/v solution of the Eudragit E100 in methylene chloride is added with mixing to the cimetidine and blended until granules are formed. The resulting granules are dried and then sieved through a 16 mesh screen.

The aluminium hydroxide, magnesium hydroxide and other ingredients for the antacid granules are sieved through a 12 mesh (1.4 mm) screen and mixed together. The resulting mix is compressed on a rotary tablet press and the resulting compacts are milled using a 12 mesh screen.

The cimetidine granules, antacid granules and extragranular excipients are put into a cone blender and mixed thoroughly. The resulting mix is discharged from the blender and compressed on a suitable rotary tablet press fitted with the appropriate punches.

EXAMPLE 2

200 mg Chewable Tablet

Ingredient	mg/tablet	%w/w
Cimetidine Premix Granules		
Cimetidine	200.0	90.9
Eudragit E100*	20.0	9.1
Antacid (Al/Mg) Granules		
	mg/tablet	%w/w
Sorbitol: Direct Compression Grade	295.0	34.01
Lactose: Direct Compression Grade		
Spray dried	162.5	18.73
Crystalline	162.5	18.73
Dried Aluminium Hydroxide Gel	125.0	14.41
Magnesium Hydroxide	100.0	11.53
Croscarmellose Sodium Type A	15.0	1.73
Magnesium Stearate	7.5	0.86
	867.5	100.00

Tableting Mix for Compression	mg/tablet		
Cimetidine Premix Granules	220.0		
Antacid (Al/Mg) Granules	867.5		
Dried Aluminium Hydroxide Gel	125.0		
Magnesium Hydroxide	100.0		
Sorbitol: Direct Compression Grade	295.0		
Lactose: Direct Compression Grade			
Spray dried	162.5		
Crystalline	162.5		
Croscarmellose Sodium Type A	45.0		
Aspartame	3.0		
Aniseed	20.0		
Butterscotch	20.0		
Magnesium Stearate	22.5	or	37.5
TOTAL	2048.0		2063.0

* Added to the cimetidine by granulation as a 40% w/v solution in methylene chloride. Solvent lost in processing.

Process Description

The cimetidine premix granules and antacid granules were prepared according to the method described in Example 1. The cimetidine granules and antacid granules were then blended with the remaining ingredients and compressed on a rotary press fitted with the appropriate tablet punches and dies. The formulations of the following Examples 3 and 4 were prepared in a similar manner.

EXAMPLE 3

200 mg Chewable Tablet

Ingredient

Cimetidine Premix Granules	mg/tablet	%w/w
Cimetidine	200.0	90.9
Eudragit E100*	20.0	9.1

Antacid (Al/Mg) Granules

	mg/tablet	%w/w
Sorbitol: Direct Compression Grade	590.0	34.01
Lactose: Direct Compression Grade		
Spray dried	325.0	18.73
Crystalline	325.0	18.73
Dried Aluminium Hydroxide Gel	250.0	14.41
Magnesium Hydroxide	200.0	11.53
Croscarmellose Sodium Type A+	30.0	1.73
Magnesium Stearate	15.0	0.86
	1735.0	100.00

Tableting Mix for Compression

	mg/tablet
Cimetidine Premix Granules	220.0
Antacid (Al/Mg) Granules	1735.0
Microcrystalline Cellulose (Avicel PH102)+	200.0
Aspartame	10.0
Aniseed	20.0
Butterscotch	20.0
Magnesium Stearate	15.0
TOTAL	2220.0

* Added to the cimetidine by granulation as a 40% w/v solution in methylene chloride. Solvent lost in processing.

\+ Croscarmellose Sodium Type A and Avicel PH102 can both be obtained from the FMC Corporation, Philadelphia PA.

EXAMPLE 4

100 mg Chewable Tablet

Ingredient	mg/tablet	%w/w
Cimetidine Premix Granules		
Cimetidine	100.0	90.9
Eudragit E100*	10.0	9.1
Antacid (Al/Mg) Granules		
	mg/tablet	%w/w
Lactose: Direct Compression Grade		
Spray dried	190.0	29.23
Crystalline	190.0	29.23
Dried Aluminium Hydroxide Gel	125.0	19.23
Magnesium Hydroxide	100.0	15.38
Croscarmellose Sodium Type A	30.0	4.62
Magnesium Stearate	15.0	2.31
	650.0	100.00

Tableting Mix for Compression	mg/tablet
Cimetidine Premix Granules	110.0
Antacid (Al/Mg) Granules	650.0
Dried Aluminium Hydroxide Gel	125.0
Magnesium Hydroxide	100.0
Sorbitol: Direct Compression Grade	590.0
Lactose: Direct Compression Grade	
Spray dried	190.0
Crystalline	190.0
Croscarmellose Sodium Type A	30.0
Aspartame	3.0
Aniseed	20.0
Butterscotch	20.0
Magnesium Stearate	15.0
Sodium Saccharin	5.0
TOTAL	2048.0

* Added to the cimetidine by granulation as a 40% w/v solution in methylene chloride. Solvent lost in processing.

CLAIMS

1. A solid pharmaceutical dosage form comprising:
(i) cimetidine; and
(ii) antacid, wherein at least part of the antacid is in the form of granules comprising a freely water-soluble solid diluent, the antacid, and a rapidly swellable water-insoluble disintegrant.

2. A solid pharmaceutical dosage form according to claim 1 wherein at least 50% of the total antacid present is contained within the granules.

3. A solid pharmaceutical dosage form according to claim 2 wherein substantially all of the antacid present is contained within the granules.

4. A dosage form according to any one of claims 1 to 3 wherein the granules are dry-granulated.

5. A dosage form according to any one of claims 1 to 4 wherein the highly water-soluble solid diluent is a sugar or a sugar alcohol.

6. A dosage form according to any one of claims 1 to 5 wherein the ratio (w/w) of solid diluent to antacid is in the range from approximately 1:1 to approximately 8:1.

7. A dosage form according to any one of claims 1 to 6 wherein the disintegrant is a cross-linked carboxymethylcellulose.

8. A dosage form according to any one of claims 1 to 7 wherein the antacid is present in an amount from between 5 mEq and 30 mEq.

9. A chewable pharmaceutical tablet composition comprising:

(i) granules comprising cimetidine and a granulating agent wherein the granulating agent is a co-polymer of dimethylaminoethylmethacrylate and methacrylic acid ester in an amount of approximately 10% (w/w) relative to the cimetidine; and

(ii) antacid-containing granules comprising aluminium hydroxide and magnesium hydroxide; a solid diluent which is lactose or a mixture of sorbitol and lactose, the ratio (w/w) of diluent to aluminium hydroxide/magnesium hydroxide being approximately 3:1; and a disintegrant which is croscarmellose sodium, the disintegrant being present in an amount of approximately 2% (w/w) relative to the total weight of the antacid-containing granules; wherein the antacid-containing granules are formed by dry granulation.

10. A granule comprising a highly water-soluble solid diluent, an antacid, and a rapidly swellable water-insoluble disintegrant as defined in any one of claims 1, 4, 5, 7 and 9.

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A3

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(31) Priority Application Number: 8710965

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(33) Priority Country: GB

(71) Applicant *(for all designated States except US)*: SMITH KLINE & FRENCH LABORATORIES LIMITED [GB/GB]; Mundells, Welwyn Garden City, hertfordshire AL7 1EY (GB).

(72) Inventors; and
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(74) Agent: HUTCHINS, M., R.; Smith Kline & French Laboratories Limited, Mundells, Welwyn Garden City, Hertfordshire AL7 1EY (GB).

(81) Designated States: AU, DK, JP, KR, US.

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(54) Title: PHARMACEUTICAL COMPOSITIONS

(57) Abstract

The invention provides a solid pharmaceutical dosage form comprising: (i) cimetidine; and (ii) antacid, wherein at least part of the antacid is in the form of granules comprising a freely water-soluble solid diluent, the antacid, and a rapidly swellable water-insoluble disintegrant. Compositions of this type overcome the problem of the reduced bioavailability of cimetidine which can occur when cimetidine is co-administered with antacids.

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INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 88/00350

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [5]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A 61 K 31/415; A 61 K 33/10; A 61 K 9/20; A 61 K 33/08

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	EP, A, 0003589 (THE WELLCOME FOUNDATION LTD) 22 August 1979, see example 1; claims 1-13	10
Y	--	1-8
Y	EP, A, 0138540 (SMITH KLINE DAUELSBERG) 24 April 1985, see page 4, lines 18-26; claims 1-10	1-8
	--	
Y	FR, M, 6885 (SMITH KLINE & FRENCH LAB.) 21 April 1969, see example 1	1-8
Y	Chemical Abstracts, vol. 102, 1985, (Columbus, Ohio, US) see page 375, abstract no. 137799m & JP, A, 59193825 (SUMITOMO CHEMICAL CO. LTD) 2 November 1984	1-8
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* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
27th July 1988	17. 01. 89
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	P.C.G. VAN DER PUTTEN

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers....., because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. Claims 1 - 8,10
2. Claim 9

for further information please see form PCT/ISA/206 mailed on 29.08.1988

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☒ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 8800350 SA 22061

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 11/01/89
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0003589	22-08-79	JP-A- 54119022	14-09-79
		AU-A- 4392179	16-08-79
		GB-A- 1601833	04-11-81
		CA-A- 1117418	02-02-82
		AU-B- 525122	21-10-82
EP-A- 0138540	24-04-85	WO-A- 8501656	25-04-85
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		DE-A- 1617800	08-04-71
		FR-A- 1515061	
		GB-A- 1129260	

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82